Diagnostic accuracy of MR Spectroscopy for grading of cerebral gliomas: a systematic review and meta-analysis

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Aims and objectives

Gliomas are the most common primary neoplasm of the central nervous system [1]. The clinical management of cerebral gliomas presents a considerable challenge, and pre-surgical grading is important for prognosis and treatment strategies [2, 3]. The reason is high grade gliomas (HGGs) are usually treated with tumor resection and additional radiation and chemotherapy, whereas in low grade gliomas (LGGs), only surgical treatment for histologic confirmation or tumor resection is performed in most patients [4-6].

Histopathological assessment is the current criterion standard for grading cerebral gliomas. However, it is sometimes difficult because of tissue heterogeneity, and stereotactic biopsy represents only a section of the tumor. Hence, imaging is essential for grading of cerebral gliomas, particularly for tumors in the eloquent areas.

MR spectroscopy (MRS) is a technique for analyzing the metabolism of organs and cells, biochemical changes and quantitative analysis of compounds in humans. Many kinds of metabolites in brain tissue, like choline compounds (Cho), N-acetylaspartate (NAA), creatine and phosphocreatine (Cr), lactate and lipid, can be tested using proton MR spectroscopy (1H-MRS). It has been reported that 1H-MRS can assess the degree of malignancy of brain tumors [7-9]. Because of differences in the cell type and growth characteristics of tumors, it is possible that tumor types or malignancy will have unique information of metabolite. Herholz K [10] and Ott D [11] two studies were performed on many series of patients and revealed the ability of 1H-MRS to give information on the basic metabolic processes in tumors. This suggests that 1H-MRS may offer important information for defining tumor characteristics.

The purpose of this systematic review and meta-analysis was to calculate the sensitivity and specificity of MRS for grading of cerebral gliomas.
Methods and materials

Search strategy

A search of PubMed for English literature was conducted for studies grading gliomas by MRS when compared to the result of histopathology, including studies listed until December 31, 2014. Using following key words and search terms: "magnetic resonance imaging", "magnetic resonance spectroscopy", "MR spectroscopy", "MRS", "1H-MRS", "glioma", "gliomas", "tumor grade", "classification" and "grading". All results were limited to English language and data extraction were conducted by two investigators independently which was achieved the consensus for all data.

Inclusion criteria for study selection

Eligible studies must meet the following inclusion criteria: (a) Studies were included if diagnostic data could be summarized in a 2×2 contingency table to estimate true positive (disease cases in which findings of the reference standard and the index test were positive for the studied target condition), false positive (non-disease cases that were misdiagnosed as diseased according to the index test), false negative (disease cases that were misdiagnosed as non-diseased according to the index test) and true negative (non-disease cases that were correctly identified with the index test) findings; (b) patients diagnosed by means of MRS; (c) biopsy and/or surgery was used as reference standard for grading of cerebral gliomas. The study did not contain sufficient details to evaluate the validity of the study were excluded. Two authors reviewed all selected abstracts to identify potential studies, and then reviewed the full text of potentially eligible papers. Disagreements were resolved by consensus.

Data extraction and quality assessment

The common information including the articles' first author, published time, mean age, number of patients, study design, detailed reference standard specifications, voxel size and spectroscopic technique were extracted. Study quality was assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [12] and individually tailored the guidelines for scoring each item in our article as suggested [13]. Positive scores of 14 items are added up and can vary from 0 to 14 [12]. Disagreement was solved by a consensus rereading of unclear points.

Statistical Analysis

The data was analyzed using Meta-Disc [14] and Stata 11.0 software. Spectroscopic classification results were tabulated against the reference standard by using 2 × 2 contingency tables.
Heterogeneity was assessed by using the Higgins and Thompson test to calculate the $I^2$ statistic [15]. This statistic is derived from Cochran's Q statistic and is more visualized to evaluate. It calculates the percentage of variation due to heterogeneity. Heterogeneity is defined to be low (0-50%), moderate (50-75%), or high (75-100%) [16].

For diagnostic accuracy, threshold analysis was confirmed to evaluate whether the diagnostic odds ratio (DOR) was constant. A symmetric summary receiver operating characteristic (ROC) curve was fitted by using the Moses constant of linear model. Measures for the analysis of summary ROC by using the area under the ROC curve (AUC) [17, 18].

Publication bias was visually assessed by producing a funnel plot with each study's log DOR plotted against its standard error of the estimate. In the Stata software, linear regression of log odds ratios on the inverse root of effective sample sizes was regarded as a test for funnel plot asymmetry. The log odds ratios were performed as the log transformed diagnostic odds ratios, which were needed for the performance of linear regression. Publication bias was consider to be present if there was a nonzero slope coefficient ($P<0.10$), revealing that only the small studies that reported a high accuracy for MRS had been published, while the small studies that reported a lower accuracy had not been published.
We identified 638 potentially relevant citations studies in PubMed and Ebsco databases. After title and abstract review, 92 studies were retrieved. After reviewing full-text studies, 84 studies were excluded because (a) no available data, (b) no comparison against reference standard. We thus selected 8 studies in our meta analysis [19-26] (Figure 1). The study characteristics are shown in Table 1. All included studies were published in English.

Fig. 1: Flowchart of study selection.

References: the second hospital of anhui medical university - Hefei/CN
Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>First Author (Year)</th>
<th>Mean Age</th>
<th>No. of patients</th>
<th>Consecutive or random sample</th>
<th>Reference standard</th>
<th>Metabolites</th>
<th>Voxels</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>QUADA Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jussi-Pekka Usenius (1996)</td>
<td>NA</td>
<td>52</td>
<td>yes</td>
<td>biopsy</td>
<td>NAA</td>
<td>NA</td>
<td>1500</td>
<td>270</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Christian Senft (2009)</td>
<td>NA</td>
<td>63</td>
<td>yes</td>
<td>biopsy</td>
<td>Cho</td>
<td>single</td>
<td>1500</td>
<td>144</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Andrés Server (2011)</td>
<td>60.6/49.0</td>
<td>74</td>
<td>yes</td>
<td>biopsy</td>
<td>Cho</td>
<td>multi</td>
<td>1500</td>
<td>135</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Maosheng Xu (2005)</td>
<td>NA</td>
<td>24</td>
<td>yes</td>
<td>biopsy</td>
<td>Cho</td>
<td>single</td>
<td>1500</td>
<td>136/144</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Q. G. Zou (2011)</td>
<td>46</td>
<td>30</td>
<td>yes</td>
<td>biopsy</td>
<td>NAA/Cr, NAA/Cho</td>
<td>single</td>
<td>1350</td>
<td>135</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>E. Kousi (2012)</td>
<td>NA</td>
<td>71</td>
<td>yes</td>
<td>biopsy</td>
<td>Cho, Cho/Cr</td>
<td>1500</td>
<td>35</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Z-L Liu (2012)</td>
<td>44.8</td>
<td>32</td>
<td>yes</td>
<td>biopsy</td>
<td>Cho, Cho/Cr, Cho/NAA, NAA/Cr</td>
<td>1500</td>
<td>144</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Jeong Hee Yoon (2014)</td>
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<td>60</td>
<td>yes</td>
<td>biopsy</td>
<td>Cho, Cho/Cr</td>
<td>2000</td>
<td>35</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>


Table 1

References: the second hospital of anhui medical university - Hefei/CN

Quality assessment

Scores of our quality assessment ranged from 10 to 12, with a mean score is 11 (Table 1). All included studies fulfilled at least 10 of 14 methodological criteria, which suggested that all included studies were of high quality.

Assessment of heterogeneity and publication bias

We calculated the I² statistic, I² = 88.18% > 50% suggested that there was a high heterogeneity of included studies. Data of heterogeneity were analyzed by selecting a bivariate random effects model that allowed for the negative correlation between sensitivity and specificity. The publication bias was assessed by using a scatter plot of the inverse of the square root of the effective sample size versus the diagnostic log odds ratio. A nonzero slope coefficient (P=0.202) showed that there was no evidence for publication bias (Figure 2).
Sensitivity and specificity values including 95% confidence intervals (CI) were calculated by using Meta-Disc software. The sensitivities ranged from 41% to 89%, and the specificity ranged from 61% to 100%. The pooled sensitivity value was 76% (95%CI=72%-80%; Q=16.69; df=15; p=0.34; I2=10.1%), and the specificity value was 83% (95%CI=79%-86%; Q=52.30; df=15; p=0.00; I2=71.3%) (Figure 3 and Figure 4). Moreover, we calculated the positive likelihood ratio (PLR) was 5.68 (95%=3.40-9.50), and the negative likelihood ratio (NLR) was 0.28 (95%=0.23-0.34). In addition, we conducted a symmetric summary receiver operator characteristic curve (SROC). The AUC of the symmetric SROC was 0.83 (Figure 5).
Fig. 3: Figure 3. Forest plot shows sensitivity from individual studies and pooled estimates.

References: the second hospital of anhui medical university - Hefei/CN
Fig. 4: Forest plot shows specificity from individual studies and pooled estimates.

References: The second hospital of Anhui Medical University - Hefei/CN
Fig. 5: Figure 5. Summary ROC curve of individual studies. 

References: the second hospital of anhui medical universitity - Hefei/CN

Ratio of Cho/Cr also analyzed in this meta-analysis. The pooled sensitivity value was 76% (95%CI=67%-84%; Q=2.17; df=4; p=0.70; I²=0.0%), and the specificity value was 79% (95%CI=72%-85%; Q=6.46; df=4; p=0.17; I²=38.1%) (Figure 6 and Figure 7). No heterogeneity was found at the patient level for both sensitivity and specificity.
Fig. 6: Figure 6. Forest plot of sensitivity of Cho/Cr and pooled estimates. 
References: the second hospital of anhui medical university - Hefei/CN

Fig. 7: Figure 7. Forest plot of specificity of Cho/Cr and pooled estimates. 
References: the second hospital of anhui medical university - Hefei/CN
Conclusion

The present meta-analysis explored the diagnostic accuracy of MR Spectroscopy for grading of cerebral gliomas. Our currently available data showed that a pooled sensitivity of 76% (95%CI=72%-80%) and a pooled specificity of 83% (95%CI=79%-86%) at the patient level. The mean QUADAS score was rather high at 11, suggesting that the included studies fulfilled most quality criteria.

Of note, we found significant heterogeneity in results among the included studies. Thus, our results should be interpreted cautiously, although we used the random effects model and a bivariate random effects meta-analysis model should correct for this issue at least in part. Use of meta-regression may explain some of the sources of heterogeneity. We also made a sub-analysis of ratio of metabolites for Cho/Cr, and no heterogeneity was found at the patient level for both sensitivity and specificity. Above all, the different metabolites and ratio of metabolites may lead the heterogeneity.

Although MRS is a useful non-invasive method for grading of cerebral gliomas in this study, it has some limitations. The local mean concentration of specific metabolite measured by MRS may be affected by heterogeneity of the tumor which increases with progression of grade. Moreover, other factors which influence efficiency of this method depend on the technical parameters of MR devices such as the MR examination protocol used, which may be different for each department. A further limitation is that only literature published in English were selected in this meta-analysis, and the population of included studies was not uniform, therefore, the results should be interpreted with caution.

In spite of the problems mentioned above, on the basis of the results of our meta-analysis, we therefore suggested MRS as an appropriate choice for grading of cerebral gliomas. For future research, it is important to improve the study design and reporting of accuracy results. When more data become available, an update of this systematic analysis and meta-analysis should be performed. We believe that, with the continuing technical development of MRI, relatively high sensitivity and specificity results can be expected.
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